and gross hematuria, suggesting papillary necrosis. Diagnosis is supported by a history of heavy analgesic use, and computed tomography (CT) may reveal microcalcifications at the papillary tips.

Treatment of analgesic nephropathy is supportive and includes discontinuation of analgesic use. Long-term follow-up studies are characterized by progression to ESRD requiring dialysis. A high incidence of uroepithelial cancers is also observed in patients with long-term analgesic use.

Chinese Herb Nephropathy and Balkan Endemic Nephropathy

Chinese herb nephropathy (CHN) and Balkan endemic nephropathy (BEN), also called *aristolochic acid nephropathy*, are chronic tubulointerstitial renal diseases associated with urothelial carcinoma. The clinical expression and pathologic lesions observed at different stages of CHN and BEN are strikingly similar except for the higher prevalence of CHN among women and familial clustering of BEN. Both have been linked to exposure to the nephrotoxin and carcinogen aristolochic acid. It has been suggested that *CHN* and *BEN* should be abandoned and replaced by the term *aristolochic acid nephropathy* (AAN).

Aristolochic acid is a major component of *Aristolochia*-containing herbal remedies and is commonly prescribed in China and other Asian countries. AAN was first reported in 1993 in Belgium in young women taking aristolochic acid–containing Chinese herbs for weight reduction, and the finding has been confirmed by many others. BEN was described 50 years ago in farming villages in the Balkan area, where there is dietary exposure to aristolochic acid through the contamination of flour prepared from locally grown wheat.

Unique features of AAN include clustering of the cases among adults in endemic areas and close association with upper urinary tract carcinomas. About 50% of the affected patients develop transitional cell carcinomas; aristolochic acid induces DNA damage with a distinct molecular signature. Unfortunately, no effective specific treatment for AAN is available. Management is supportive with regular monitoring for urothelial malignancy.

Heavy Metals

Heavy metals such as cadmium, lead, and chromium can cause CIN, and exposure usually represents an environmental toxin. Cadmium exposure occurs with tobacco smoke and contaminated water and food. Lead exposure occurs from contact with lead-based paint and lead-contaminated dust and soil. Chromium is used to increase the hardness and corrosion resistance of alloy steel, and chromium exposure can occur when industrial plant employees work with alloy steels, dyes, paints, inks, and plastics. Renal proximal tubules are the principal site of accumulation and injury, but other nephron segments also can be injured.

Heavy metal nephrotoxicity ranges from mild tubular dysfunction to severe renal failure. The extent of renal damage depends on the nature, dose, route, and duration of exposure. With chronic exposure, changes consistent with CIN are observed on kidney biopsy. The best characterized clinical feature of heavy metal renal toxicity is the Fanconi syndrome, which results from proximal tubule damage. These patients have low-molecular-weight proteinuria, aminoaciduria, bicarbonaturia, glycosuria, and phosphaturia. Other clinical findings for lead toxicity include gout from decreased urate excretion in proximal tubules, hemolytic anemia, encephalopathy, and neuropathy.

Other than supportive care, no specific treatment is available for heavy metal–associated renal disease. Chelating agents may be used in acute poisoning, but no randomized clinical trials have proved the efficacy of chelation on clinical outcomes.

Sarcoidosis

Sarcoidosis is a chronic, multisystem, inflammatory disease of unknown origin. It is characterized by noncaseating, epithelioid granulomas in affected organs, leading to organ dysfunction. The severity and diversity of the clinical manifestations related to sarcoidosis depend on the extent of the infiltrating granulomatous lesions. Granulomatous tubulointerstitial nephritis is observed in approximately 20% of patients with sarcoidosis and responds well to steroid therapy. Sarcoidosis is described in details elsewhere.

Steroid therapy is effective in the acute setting and in advanced tubulointerstitial nephritis. Some patients with granulomatous tubulointerstitial nephritis may require long-term treatment with steroids to preserve renal function, although the side effects of steroids limit their use in advanced renal disease. The efficacy of steroid-sparing agents such as mycophenolate mofetil or azathioprine requires further investigation.

Radiation Nephritis

Radiation exposure is a significant cause of chronic kidney disease, and radiation nephritis develops in most patients if they are exposed to more than 2300 cGy. Ionizing radiation directly damages all molecules, including DNA, and initiates cellular synthesis of reactive oxygen species (ROS), which cause secondary tissue damage. Hydroxyl radicals are generated within milliseconds of tissue exposure. Oxidative stress and other factors may play additional roles over time, and patients may develop severe renal injury and impaired function 6 to 12 months (or longer) after exposure.

The diagnosis is based on a history of radiation exposure and the clinical findings of renal injury. Treatment is supportive.

Sickle Cell Disease

Chronic renal insufficiency is relatively common in patients with sickle cell disease, an inherited hematologic disorder characterized by hemolytic anemia and vascular occlusion by sickled red cells. Under normal conditions, the renal medullary zone is characterized by low oxygen tension, acidic pH, and high osmolality, which can predispose to increased blood viscosity and red blood cell sickling. This increases the likelihood of local ischemia and infarction of the renal microcirculation. In the vasa recta, vascular occlusion can interfere with the countercurrent exchange system in the inner medulla, resulting in a defect in the urine-concentrating mechanism.

Patients may have nocturia or polyuria and can develop gross hematuria due to papillary necrosis resulting from medullary ischemia and infarction. The sloughed papillae can obstruct urinary tract outflow, leading to obstructive nephropathy and renal failure. Another renal abnormality associated with sickle